REMARKS

The Claimed Invention

The claimed invention is directed to methods for producing conformer specific monoclonal antibodies and to conformer specific antibodies and fragments thereof.

The Pending Claims

Prior to entry of the above amendments, Claims 12-14 and 51-53 are pending. Claims 12 and 53 are directed to methods for producing conformer specific monoclonal antibodies; Claim 13 is directed to monoclonal antibodies; and Claim 14 is directed to binding fragments from the conformer specific monoclonal antibodies.

The Office Action

Claims 12-14 and 51-53 stand rejected under 35 U.S.C. §112 second paragraph, as being indefinite.

Claims 12-14 and 51-53 stand rejected under 35 U.S.C. §112 first paragraph, as not meeting the written description requirement.

Claims 12-14 and 51-53 stand rejected under 35 U.S.C. §112 first paragraph, as not being enabled by the specification.

Response to the objections and rejections

In the response that follows, the Examiner's individual objections and rejections are provided in full text, as identified by indented small bold print, followed by Applicant's response.

35 U.S.C. §112 Second Paragraph Rejection

Claims 12-14 and 51-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "conformer" renders the claims indefinite because the ordinary artisan would not know what is meant by this term. Does "conformer" refer to the immature capsid in association with HP68 or does conformer refer to a mutant of HP68. The phrase "conformer" renders the claims indefinite because the specification doe (sic) not provide some standard of

measuring the degree intended by the term, thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05.

This rejection is respectfully traversed because applicants do indeed provide a definition of the term conformer: *"The term "conformer" refers to a protein having at least substantially the same amino acid sequence, but heterogeneity in structure (physical topology or topography) and function. By topology is intended the different placement of the protein, e.g. C-cytosolic as compared to N-cytosolic, and topography intends change in external conformation or shape, (i.e different three-dimensional shape due to differences in folding/conformation), which includes stable and transient association with other proteins. As used herein, polypeptides of substantially the same amino acid sequence are those with conservative amino acid substitutions (i.e. a small or large side chain for a small or large side chain, respectively; or an acidic, basic, polar or hydrophobic side chain for an acidic, basic, polar or hydrophobic side chain, respectively), that do not alter the protein conformation or topology. The protein conformation changes are due to post-translational modifications and are not a factor of the amino acid sequence."* Specification, page 8, line 26 through page 9, line 3.

The term conformer thus does not refer to the immature capsid in association with HP68 nor does the term conformer refer to a mutant of HP68. Rather, the term refers to any protein which exists in two or more different tertiary structures which also exhibit differences in function. Conformers are like twins which, based on appearance (amino acid sequence) seem to be identical, but their ability in sports (function) is different, one is good at tennis and the other is good at baseball. Neither one would be considered a mutant of the other; rather they are functionally different versions of the same genetic material.

HP68 is an example of a protein which has two or more conformational forms, two of which have been identified based on differences in function. A first conformer of the HP68 protein is known that associates with and inhibits RNase L, a cellular protein that is upregulated by interferon, binds to ribosomes, and promotes degradation of viral RNA (Zhou *et al.* Cell (1993) 72:753-65; Player *et al.* Pharmacol Ther (1998) 78:55-113; Samuel C. Virology (1991) 183:1-11; Sen *et al.* JBC (1992) 267:5017-20). Applicants show in Figure 14, that there is a second conformer of the HP68 protein that facilitates HIV-1 capsid formation binds HIV-1 Gag

and Vif proteins but does not bind RNase L in human cells, which have been transfected with plasmids expressing Gag alone or with the plasmid pBRUΔenv. Thus there are two conformers of HP68 that not only act by two different mechanisms but reside in two different complexes in host cells as well. In this case the demonstrated functions of the two HP68 conformers both promote viral replication, one specifically for HIV, the other for viruses in general. The term conformer does not render the claims indefinite and the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §112 First Paragraph Written Description Rejection

Claims 12-14 and 51-53 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a method of making monoclonal antibodies, these antibodies are to the chaperone protein involved in the capsid assembly but not the conformer that does not bind gag. The specification has disclosed the production of polyclonal antibodies to wheat germ derived and human derived C-terminal HP68 peptide sequences. The method (claim 12) requires the use of a knockout mouse to produce these antibodies. Neither the specification nor the prior art has provided any teaching regarding such a knockout animal. The specification also has not disclosed any monoclonal antibodies.

This rejection is respectfully traversed because both the specification and the prior art provide teaching regarding the production of knockout animals. Knockout mice can be produced using standard techniques known to those skilled in the art for more than ten years (Capecchi, Science (1989) 244:1288; Koller et al. Annu Rev Immunol (1992) 10:705-30; Deng *et al.* Arch Neurol (2000) 57:1695-1702).

The claims are directed to methods and compositions obtained thereby for developing conformer specific antibodies by immunizing knock-out mice that lack a functional gene for the protein of interest with a putative conformer of the protein of interest. The specification describes how the gene corresponding to the protein against which monoclonal antibodies are to be raised is knocked out, e.g. HP68. A targeting vector is constructed which, in addition to containing a fragment of the gene to be knocked out, generally contains an antibiotic resistance gene, preferably neomycin, to select for homologous recombination and a viral thymidine kinase

(TK) gene. Alternatively, the gene encoding diphtheria toxin (DTA) can be used to select against random insertion. The vector is designed so that if homologous recombination occurs the neomycin resistance gene is integrated into the genome, but the TK or DTA gene is always lost. Murine embryonic stem (ES) cells are transfected with the linearized targeting vector and through homologous recombination recombine at the locus of the targeted gene to be knocked out. Murine ES cells are grown in the presence of neomycin and gancyclovir (for TK), a drug that is metabolized by TK to produce a lethal product. Thus cells that have undergone homologous recombination are resistant to both neomycin and gancyclovir. Vectors containing DTA kill any cell that codes for the gene, so no additional drug is required in the cell culture medium. Southern blotting hybridization and PCR are used to verify the homologous recombination event, techniques well known to those skilled in the art.

To generate a mouse carrying a disrupted targeted gene, positive ES cells are propagated in culture to differentiate and the resulting blastocyte is implanted into a pseudopregnant female. Alternatively the ES cells are injected back into the blastocoelic cavity of a preimplantation mouse embryo and the blastocyte is then surgically implanted. The transfected ES cells and recipient blastocytes can be from mice with different coat colors, so that chimeric offspring can be easily identified. Through breeding techniques homozygous knockout mice are generated. Tissue from these mice is tested to verify the homozygous knockout for the targeted gene, for example using PCR and Southern blotting hybridization.

Creating new, genetically engineered animal research models involves two transgenic techniques. (1) the classical pronuclear microinjection: introduction of foreign DNA into embryonic pronuclei resulting in random integration and (2) expression and embryonic stem (ES) cell-mediated gene targeting: introduction of genetically modified ES cells into recipient embryos resulting in the ablation (knockout) or modification of a specific gene expression (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4). All transgenic models, whether targeted or untargeted, may still present unpredictable expression patters due to incomplete knockout of the targeted gene, redundancy within the genome or unanticipated genetic interactions, such as down-regulation of other genes. (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4).

The issues raised by the Examiner are not relevant for the production of monoclonal antibodies to a conformer of interest. Applicants clearly were in possession of the subject matter

of the claimed methods and compositions . Claims 12-14 are originally filed claims and as such demonstrate that the applicants were in possession of the claimed subject matter at the time the subject application was filed. To make animals that lack a functional gene for a protein of interest, for example HP68, they described polyclonal antibodies with which to screen knockout animals to confirm that the animals are not making HP68. Animals that are confirmed as non-producers of HP68 are then immunized with a conformer of HP68 and standard techniques for preparing monoclonal antibodies followed. The conformers that are used for immunization have already been isolated, namely the conformer that binds to Gag but not to RNAseL and the conformer that binds to RNAseL and not to Gag. The amino acid sequence of the proteins was already known.

The claims encompass a genus of compounds (monoclonal antibodies) defined only by their function wherein the relationship between the structural features of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was Already (sic) for patenting" such as by the use of drawings or structural chemical formulas that show the invention was complete, or describing distinguishing identifying characteristics sufficient to show that the applicant was in Possession (sic) of the claimed invention.

Claimed invention is drawn to an antibody identified by the method of claim 12. However, no structural or specific functional characteristics of such an antibody is provided, nor is there any indication that the artisan actually implemented the method of claim 12 so as to identify any monoclonal antibodies. This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2nd 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

The Examiner here raises a straw man. The skilled artisan does not need to know the structural

features of the monoclonal antibodies in order to know whether any given monoclonal antibody falls within the scope of what is claimed. It does not constitute undue experimentation to evaluate a given antibody based upon its function, namely whether or not a given monoclonal antibody binds to Gag and to one of the conformers of HP68. Skilled artisans in the monoclonal antibody area are used to screening many thousands of possible antibodies in search of those with the desired characteristics. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §112 First Paragraph Enablement Rejection

Claims 12-14 and 51-53 rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to a method of making monoclonal antibodies, these antibodies are to the chaperone protein involved in the capsid assembly but not the conformer that does not bind gag. The specification has indicated the production of polyclonal antibodies to wheat germ derived and human derived C-terminal HP68 peptide sequences. The method (claim 12) requires the use of a knockout mouse to produce these antibodies. Neither the specification nor the prior art has provided any teaching regarding such a knockout animal. The specification also has not disclosed any monoclonal antibodies.

Creating new, genetically engineered animal research models involves two transgenic techniques. (1) the classical pronuclear microinjection: introduction of foreign DNA into embryonic pronuclei resulting in random integration and (2) expression and embryonic stem (ES) cell-mediated gene targeting: introduction of genetically modified ES cells into recipient embryos resulting in the ablation (knockout) or modification of a specific gene expression (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4). All transgenic models, whether targeted or untargeted, may still present unpredictable expression patterns due to incomplete knockout of the targeted gene, redundancy within the genome or unanticipated genetic interactions, such as down-regulation of other genes. (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4). Indicating that until an animal has actually been created there is a high degree of uncertainty.

To comply with the enablement requirement of 35 U.S.C.§112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ. 1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability of lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The instant fact pattern fails to disclose any particular structure for the claimed monoclonal antibody that requires the use of a knockout animal to create. The specification does not provide any guidance or any working examples

in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed antibody without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C.§112 first paragraph

This rejection is respectfully traversed because how to make and how to use knockout mice has been known to the art for more than ten years. *See* Capecchi, Science (1989) 244:1288; Koller et al. Annu Rev Immunol (1992) 10:705-30; and Deng *et al.* Arch Neurol (2000) 57:1695-1702. Furthermore, it is not the structure of the monoclonal antibody that is important per se but rather the three dimensional structure of the protein conformer used to generate the monoclonal antibody that is significant. What is important about the monoclonal antibody is that it bind to an epitope on that three dimensional structure such that renders the monoclonal antibody substantially specific for one of the conformers of the protein of interest and therefore can be used to distinguish among them.

Describing how to make a knockout mouse and what to immunize it with in order to make the claimed monoclonal antibodies is not describing how to find the claimed monoclonal antibodies, but instead is describing how to make and how to use them. Furthermore, not only is the methodology behind the claimed methods and compositions well known to those of skill in the art, but it is described in considerable detail in the subject application. The present application provides not only standard protocols to produce knockout mice and monoclonal antibodies but also provides how to isolate the proteins that are used as immunogens. The claimed methods, and antibodies made thereby, employ readily available sources or are derived from readily available starting materials through routine screening that does not require undue experimentation. Accordingly, the specification does meet the enablement requirement and the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (831) 648-3090.

Respectfully submitted,

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